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Regulation of Radiopharmaceuticals – what is required for a good clinical application

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radiopharmaceuticals

Radiopharmaceuticals are classified as medicinal products and their production, indications and use are regulated accordingly.

- **pharmaceuticals**
- generally administered via intravenous route
- Conditionally released before all QC results are available
- Produced just-in-time (no supply redundancy)
- **Diagnostics :** no (side) effects anticipated (small mass amounts)
- **Therapeutics :** potential side effects

GMP also applies to radiopharmaceuticals!

European Commission has issued European directives setting normative standards, **while the European Medicines Agency (EMA)** is in charge of the review and approval of marketing authorization applications.

In every single (EU) member state there is also national legislation on medicinal products that refers to the EU directives and in some instances to regulations issued by the national competent authorities.
Despite their shared references to the relevant EU directives, **national regulations are not exactly equivalent to each other.**

The legal conditions relating to the production of radiopharmaceuticals for clinical trials, and in particular the required compliance with the principles of good manufacturing practice (GMP), have not been clear and there has been variation between EU member states.

With the intention of overcoming the general negative effects that derived from the old Directive 2001/20 concerning clinical trials, on 27 May 2014 the European Commission issued a new regulation (**No. 536/2014**) (Official Journal of European Union, 2014).
Since a “regulation” of the EU **is to be adopted as national law without any changes**, it is more stringent than a “directive”, which requires transposition into the national body of laws.

Within this new clinical trial regulation, there are three relevant points regarding the preparation of radiopharmaceuticals for clinical trials:

1) **Authorisation is no longer needed for the manufacture of diagnostic investigational radiopharmaceuticals** for use in hospitals taking part in the same clinical trial based in the same EU member state.

2) **GMP production according to EudraLex 4 is no longer required for diagnostic radiopharmaceuticals even in the case of investigational medicinal products (IMPs),** but can still be imposed by local (national) regulations.

3) **Simplified labelling of the primary packaging is allowed**, solving the issue of the need to provide too much information on the primary packaging label.

The regulation is applicable only to diagnostic IMPs and non-IMPs; therapeutic IMPs and non-IMPs are excluded.

Investigational Medicinal Products (IMPs)

“Medicinal products” are defined by Directive 2001/83/EC as "…*prepared industrially or manufactured by a method involving an industrial process*…".

Radiopharmaceuticals which may be classified as IMPs include radiolabelling kits, radionuclide generators and radionuclide precursors.

EU **Investigational Medicinal Product (IMP) Safety documentation requirements for radiopharmaceuticals** [radionuclide generators, kits, radionuclide precursor radiopharmaceuticals and industrially prepared radiopharmaceuticals] :
Standard requirements for medicinal products [= ICH M3(R2) for preclinical safety]
Radiation dosimetry - Organ/tissue exposure to radiation; - Absorbed radiation dose estimates for a given route of administration according to a specified, internationally recognised system.

(http://ec.europa.eu/health/files/pharmacos/docs/doc2006/07_2006/def_imp_2006_07_27_en.pdf)

Therapeutic Radiopharmaceuticals Studies should be designed to assess:

- the *in vivo* stability of the radionuclide complex;
- the animal biodistribution of the radionuclide;
- the potential chemical toxicity;
- the radiation exposure of tissues.

For therapeutic radiopharmaceuticals, safety is determined by the margin between - the dose exceeding organ tolerance or inducing late radiation toxicity, and - the minimum efficacious dose

Therapeutic Radiopharmaceuticals Single-dose toxicity: These studies may give some indication of the likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing in the relevant animal species

Reproductive function and foetal toxicity: Studies may be required in certain cases, especially if the radiopharmaceutical is intended for repeated use in women of child-bearing potential. Otherwise the study on reproductive function may justifiably be limited to ascertaining the effect on fertility.

Mutagenic potential: Characterization of the mutagenic potential of the non-radioactive equivalent of the product; may be limited to screening for gene and chromosome mutations.

Carcinogenic potential: An evaluation of any carcinogenic potential of the substances involved must be presented. If no carcinogenicity tests are performed, this must be clearly indicated.

EU Legislation: Eudralex

PUBLIC HEALTH

European Commission

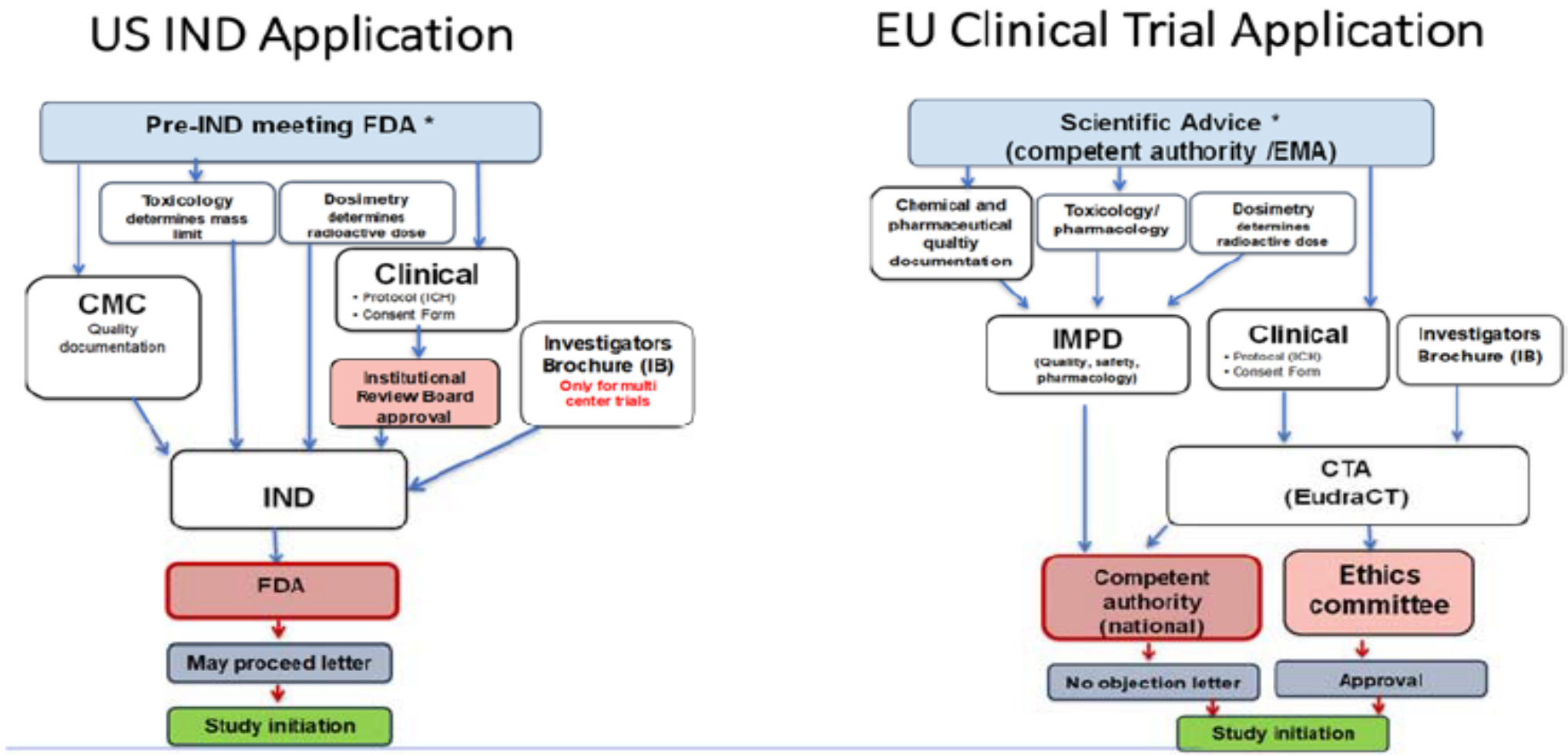
EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guideline

- Part I: Medicinal Product
- Part II: Active Pharmaceutical Ingredients
- Part III: GMP related documentation

  - Annex 1: Sterile Manufacturing Products
  - Annex 3: Radiopharmceuticals
  - Annex 13: Manufacturing of investigational products
  - Annex 15: Validation and Qualification

https://ec.europa.eu/health/documents/eudralex/vol-4_en

Application process for a Clinical Trial, comparing the current situation in Europe and USA



* Not obligatory

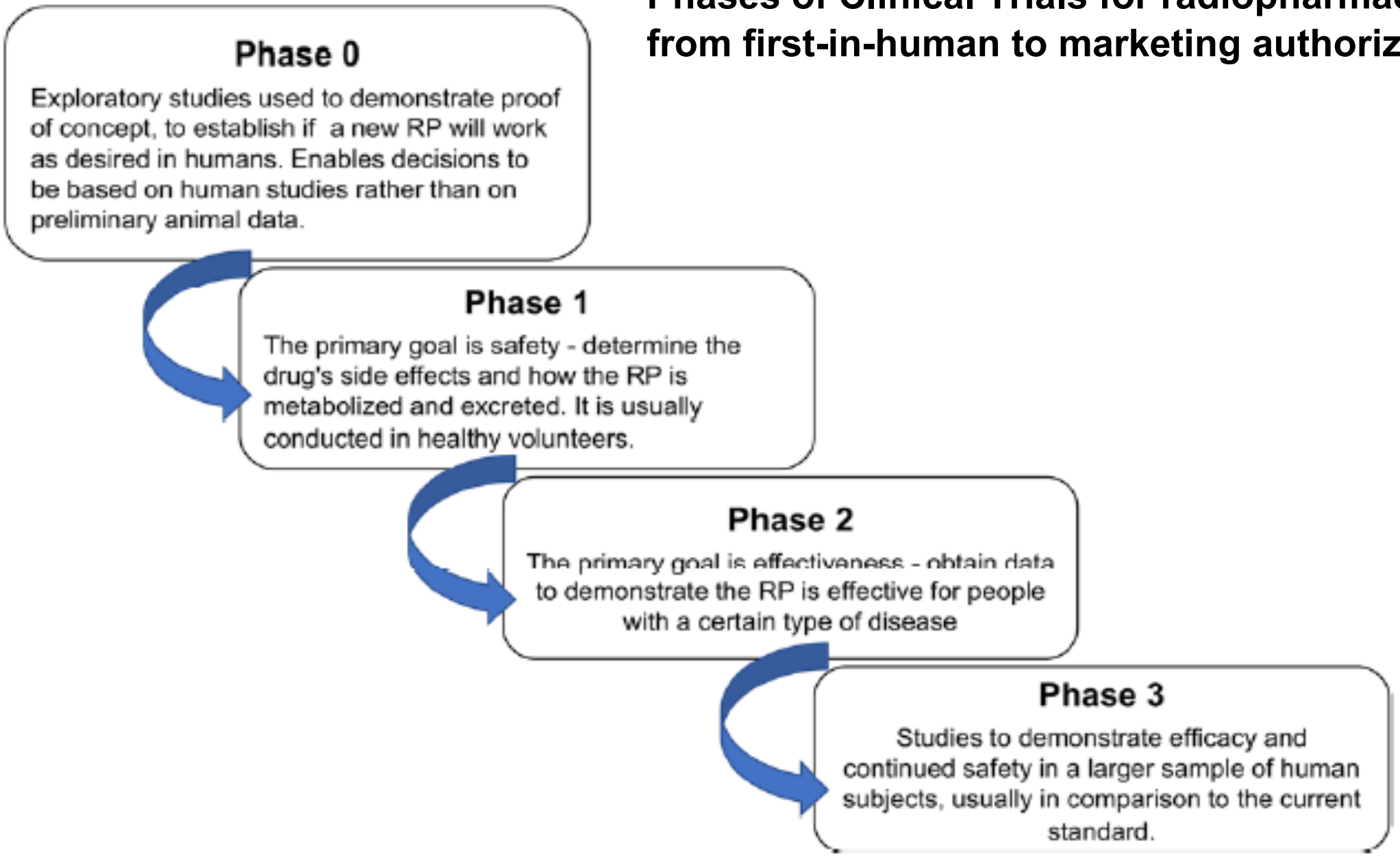
Formal Requirements for Clinical Trials

Jurisdiction	US	Europe (current)	Europe (proposed)
Regulations	21CFR 50, 54, 56 & 312	Directive 2001/20/EC , 2005/28/EC, 2003/94/EC	REGULATION (EU) No 536/2014
Submission Structure	Single IND with clinical amendments for new protocols	Per study	Per study
Submission Format	eCTD for commercial IND Non-eCTD for non-commercial IND	Non-eCTD electronic (paper cover letter + CD)	eCTD ("EU-portal")
Regulatory Approval Time	30 days (initial study), 0-30 days subsequent amendments	60 days, variable for EC approval	10 + 50 days
Labels	Investigational use statement	Sponsor, EudraCT-Nr Investigational Use statement	Simplified for diagnostic RPs
Annual Report	Required	N/A	N/A
Fees	None	National	National
Ethics Approval	Required (IRB)	Required (EC)	Integrated in centralized evaluation process
Database	www.clinicaltrials.gov	European Clinical Trial database (EudraCT), EU Clinical Trials Register (EU CTR)	European Clinical Trial database (EudraCT), EU Clinical Trials Register (EU CTR)
Record Retention	2 years post FDA Approval or after last patient administration Notify FDA	5 years after completion of trial (in certain cases up to 30y)	25 years (for Advanced Therapy Medicinal Products 30 years)
Financial Disclosure	Required	N/A	N/A
Safety Reporting to Authority	Life-threatening SUADR 7d SUADR 15d	Life-threatening SUADR 7d (+8d follow up) SUADR 15d	Life-threatening SUADR 7d (+8d follow up) SUADR 15d

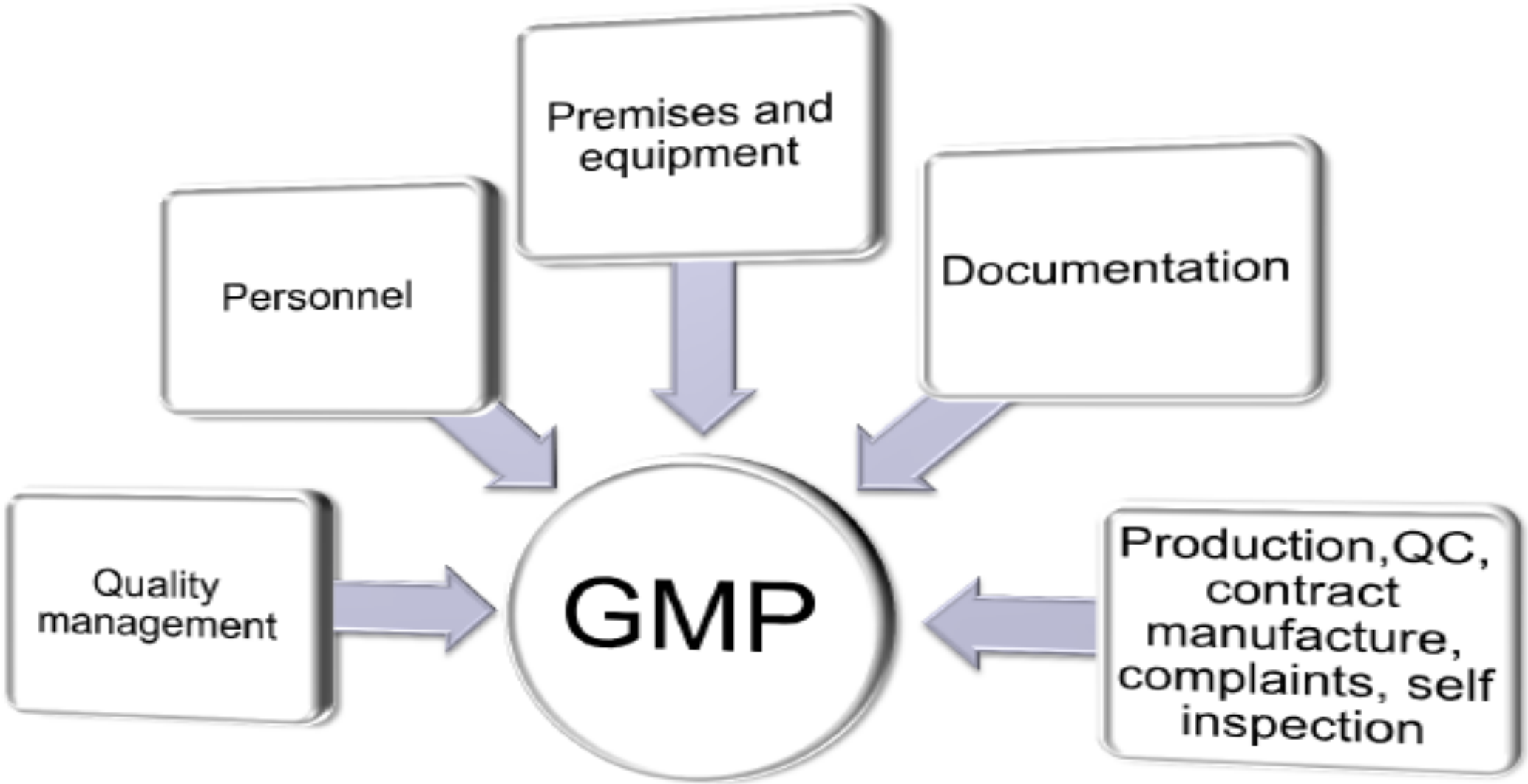
Documentation Required for Clinical Trials

Jurisdiction	US	Europe
Submission name	Investigational New Drug Application (U.S)	Clinical Trial Application (EU)
General	Form FDA 1571	EudraCT Registration
	Table of Contents	CTA-application Form for Competent Authority and Ethics Committee
	Introductory Statement	
Related to Clinical Trial conduct	General Investigation Plan	Protocol synopsis
	Clinical Protocol	Clinical Trial Protocol
	Informed Consent Form	Informed Consent Form
	Case Report Forms, SOPs, …..	Case Report Forms, SOPs, …..
Related to Radiopharmaceutical	Investigator's Brochure	Investigator`s Brochure
	Chemistry Manufacturing and Controls (CMC)	Investigational Medicinal Product Dossier (IMPD) including quality, pharmacology, toxicology and clinical data of the IMP
	Pharmacology and Toxicology Data	
	Previous Human Experience Clinical Reports	
Others	Dosimetry Letter of Access to cross-referenced IND or Master File (If applicable)	Additional information (Facility and staff, financial issues (Insurance, compensations, agreements))

Phases of Clinical Trials for radiopharmaceuticals, from first-in-human to marketing authorization



Where is the place of Good manufactering practices (GMP) ?



Where is the place of Good manufactering practices (GMP) ?

GMP = quality management system for pharmaceutical products ensuring consistent (for every batch)

- **Production**
- **Control (QC)**

appropriate to their intended use in agreement with product specification.

- **clinical trial authorization (IMPD)**
- **marketing authorization**

cGMP= current good manufacturing practice
(dynamic continuously evolving)

Why Good manufactering practices (GMP) ?

Reduce health hazard for patients

- toxicity/side effects
- lack of therapeutic/diagnostic effect
- supply gaps

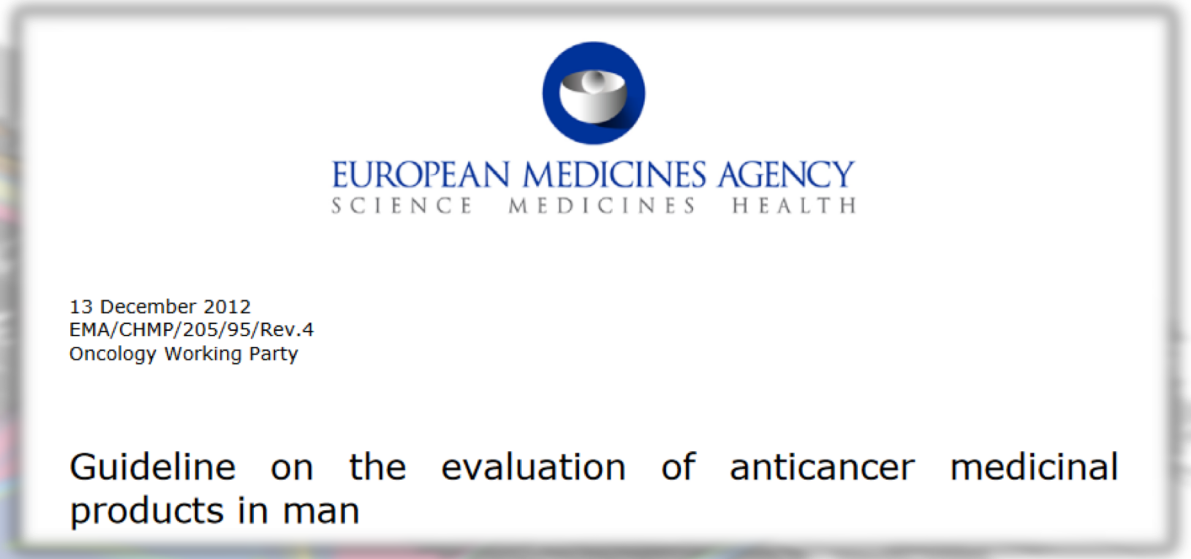
Preventive actions (validation, documentation, training,...)

Curative actions (change control, root cause investigations,...)

Radiopharmaceuticals for therapy

Additional radiopharmacological risk

Important to check identity, radiochemical & radionuclidical purity, stability (radiolysis) *in vitro* and *in vivo*


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CHMP/205/95/Rev.4
Oncology Working Party

Guideline on the evaluation of anticancer medicinal products in man


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

December 2009
EMA/CPMP/ICH/286/1995

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals

Step 5

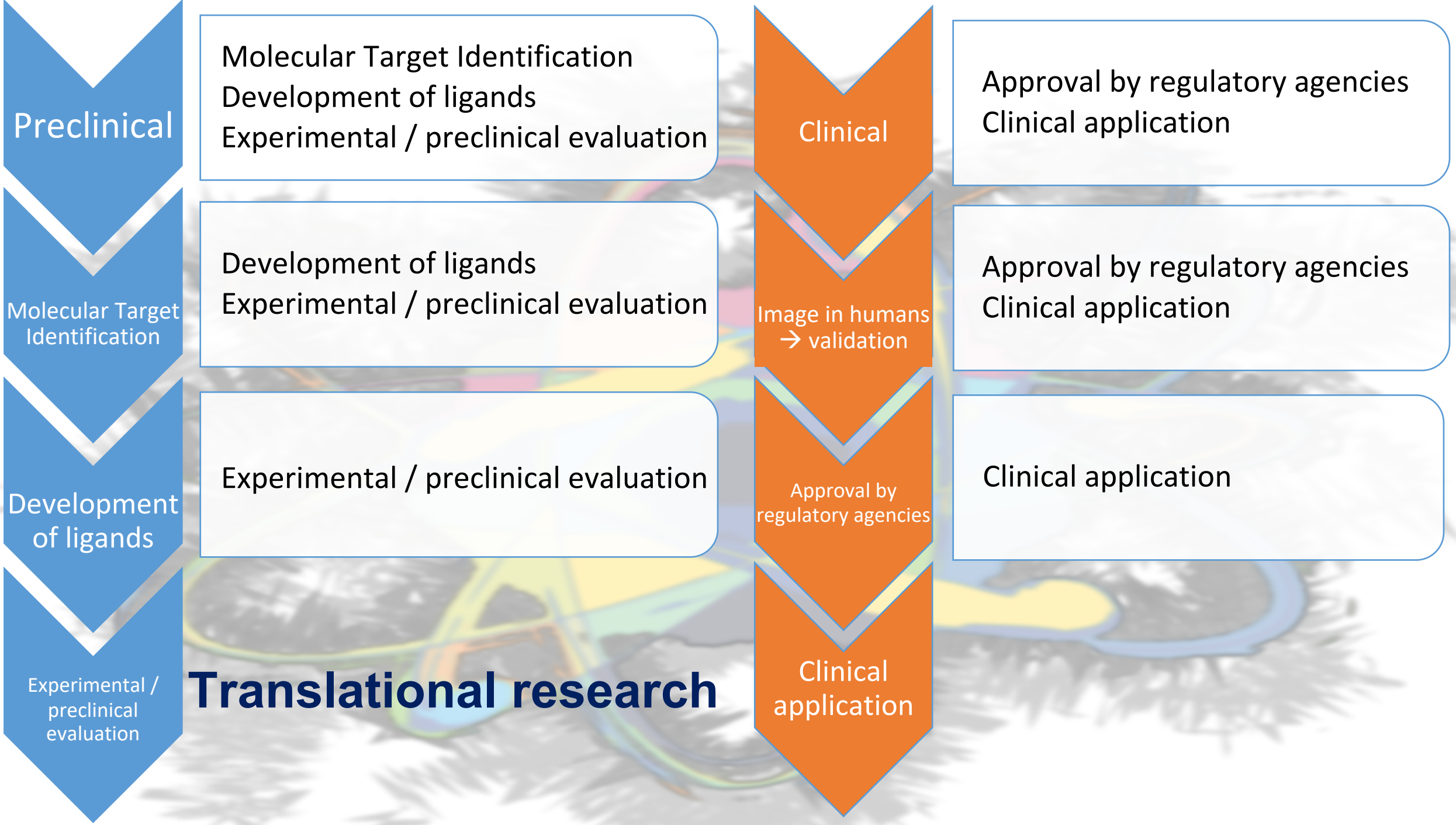
Radiopharmaceuticals for therapy toxicological testing?

Exploit theranostic advantage:
prediction of toxicity/side effects from:

- **physicochemical properties** (radionuclide decay particle energy, half-life, affinity, microdistribution (microdosimetry) in target and non-target tissue, in-vivo stability
- **Companion diagnostic**: individual real-time dosimetry

Modeling and treatment planning (similar to external radiotherapy) and evaluation of tumor response
Relevance of toxicological testing in small animals?
Single toxicological test for theranostics pairs?

“microdosing” applicable for diagnostic radiopharmaceuticals (<100 µg) 100 fold dose 14 day study in single species (rats/mice)


Preclinical
Molecular Target Identification
Development of ligands
Experimental / preclinical evaluation
Molecular Target Identification
Development of ligands
Experimental / preclinical evaluation
Development of ligands
Experimental / preclinical evaluation
Experimental / preclinical evaluation
Translational research
Clinical
Approval by regulatory agencies
Clinical application
Image in humans → validation
Approval by regulatory agencies
Clinical application
Approval by regulatory agencies
Clinical application
Clinical application

CONCLUSIONS:

The EU regulation 536/2014 aims to facilitate the experimental use of diagnostic radiopharmaceuticals in particular regarding GMP requirements and needs to be applied

The application is still far from being completed due to national restrictions that are conflicting with the content of the above EU regulation

Although the nuclear medicine centres are obliged to be compliant with national regulatory, national authorities have to be required to work towards full application of the new regulation, in particular concerning GMP production for diagnostic radiopharmaceuticals in clinical trials

An update of 536/2014 that includes therapeutic radiopharmaceuticals could be matter of fruitful open discussion involving EMA and European Commission for a rational and safe advance of nuclear medicine

Thank you